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Effect of Renin–Angiotensin System Inhibition on Cardiovascular Events in Older Hypertensive Patients with Metabolic Syndrome

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ABSTRACT

Objective. Metabolic syndrome (MetS) is associated with cardiovascular disease (CVD). Insulin resistance has been hypothesized as the underlying feature of MetS. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are widely used antihypertensives that may improve insulin sensitivity. The aim of the study is to evaluate the effect of ACEI/ARB on incident CVD events in older hypertensive patients with MetS.

Materials/Methods. We used the Cardiovascular Health Study, a prospective cohort study of individuals > 65 years of age to evaluate ACEI/ARB use and time to CVD events (including coronary and cerebrovascular events). The study included 777 subjects who had hypertension and ATP III-defined MetS, but free of CVD and diabetes at baseline. Cox regression models were used to evaluate the effect of ACEI/ARB as compared to other antihypertensives on the time to the first CVD events.

Results. ACEI/ARB use was associated with a decreased risk of CVD events (adjusted HR = 0.658, 95 % C.I. [0.436–0.993]) compared to other antihypertensives. When CVD endpoints were evaluated separately, use of ACEI/ARB was associated with lower rates of angioplasty and coronary events (HR of 0.129 and 0.530 respectively, with 95 % CI [0.017–0.952] and [0.321–0.875]).

Conclusions. ACEI/ARB use was associated with a lower risk of CVD events in older hypertensive patients with MetS, primarily due to a reduction in coronary events. The potential protective effect of ACEI/ARB on CVD events in older individuals with MetS will need further confirmation from prospective studies.

Abbreviations: NCEP, National Cholesterol Education Program; ATP, Adult Treatment Panel; MetS, metabolic syndrome; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHS, Cardiovascular Health Study; NHLBI, National Heart Lung and Blood Institute; MI, myocardial infarction; CHF, congestive heart failure; TIA, transient ischemic attack; CABG, coronary artery bypass graft; HR, hazard ratio; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; LIFE, Losartan Intervention for Endpoint Reduction; EUROPA, European Trial on Reduction of Cardiovascular Events with Perindopril in Stable Coronary Artery Disease; HOPE, Heart Outcomes Prevention Evaluation.

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1. Introduction

Metabolic syndrome (MetS), a constellation of metabolic risk factors, increases the risk for diabetes and cardiovascular events [1–3], including cardiovascular disease mortality [4–6], all-cause mortality [4–6], and coronary heart disease mortality [6]. The pathogenesis of MetS is complex and incompletely understood, but obesity and insulin resistance contribute to its development [7].

The National Cholesterol Education Program's (NCEP) Adult Treatment Panel III (ATP) criteria represent the most widely used definition for MetS. MetS, as defined by the ATP III criteria, is estimated to be prevalent in 28% of US adults [8]. The prevalence of MetS increases with age, reaching peak levels in the sixth decade for men and the seventh decade for women [9].

Current pharmacologic management of MetS focuses on the specific risk factors without targeting the underlying insulin resistance [10]. Several lines of evidence suggest that the renin–angiotensin system is both a contributor and target for several risk factors associated with the metabolic syndrome [11]. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) may improve insulin sensitivity [12–14], decrease the risk of type 2 diabetes [15], improve endothelial function [16], and reduce atherosclerosis and cardiovascular disease risk [17]. Whether ACEI and ARB improve clinical cardiovascular outcomes in hypertensive older patients with MetS is yet to be investigated. The purpose of this study is to evaluate the association between the use of ACEI/ARB and incident cardiovascular events in older adults with hypertension and MetS.

2. Methods

2.1. Data Source

We used data from the Cardiovascular Health Study (CHS), a community-based prospective cohort study conducted by the National Heart Lung and Blood Institute (NHLBI) in adults aged 65 and older, to evaluate risk factors for the development and progression of cardiovascular events. The purpose and design of CHS have been published previously [18]. Briefly, the CHS consisted of over 5800 participants randomly selected from Medicare eligibility lists in four U.S. communities in North Carolina, California, Pennsylvania and Maryland. Data collected included demographics, current medication use, blood pressure, medical history, lifestyle habits, anthropometric measures, fasting blood chemistry, echocardiography, electrocardiography and carotid ultrasonography. For each cardiovascular condition at baseline, data from self-report were confirmed using components of the baseline examination and a validation protocol that included review of medical records and confirmation by treating physicians [19]. University of Vermont's Central Blood Analysis Laboratory analyzed each participant's blood chemistry, which was drawn in the morning after an overnight fast. Further details on laboratory and blood sampling procedures, examinations, and quality assurance protocols have been published previously [18,20–22]. Subjects were followed with annual clinic visits and interim 6-month phone calls for a total of 11 years, followed by telephone follow-ups only from year 11 to 15. For this analysis, we used only the first 11 years of validated event data, as data for cardiovascular events after year 11 were obtained from telephone self report without validation from medical records. The CHS was approved by the University of Washington's Data Coordinating Center and the investigational review boards at all locations. Analysis of CHS data for the purpose of evaluating the association between ACEI/ARB use and incident cardiovascular events was approved by the Virginia Commonwealth University Institutional Review Board.

2.2. Inclusion and Exclusion criteria

The subjects included in the present analyses included individuals from CHS who had used any antihypertensive medication during the study. In addition, these subjects met the ATP III criteria for MetS [10]. We excluded subjects with baseline diabetes (defined as having a fasting blood glucose $\geq$ 126 mg/dl or a 2-h serum glucose $\geq$ 200 mg/dl upon an oral glucose tolerance test with 75 g glucose, or use of diabetes medications). Subjects with a history of cardiovascular events, including myocardial infarction (MI), congestive heart failure (CHF), coronary heart disease, claudication, stroke, transient ischemic attack (TIA), angina and arrhythmia, were also excluded. Individuals with prevalent cardiovascular disease and diabetes were excluded because they were already at risk for cardiovascular events regardless of the presence of MetS. We then classified the subjects based on their exposure to ACEI or ARB during the study. Hence, the exposed group was composed of individuals who had used ACEI/ARB alone or combined with other anti-hypertensives, and the control group represented those who took anti-hypertensives other than ACEI/ARB.

2.3. Endpoints

The primary endpoint was defined as the occurrence of *any* first cardiovascular event, including incident MI, silent MI documented by electrocardiogram, stroke, TIA, angioplasty, coronary artery bypass graft (CABG) procedures, angina, claudication, or death due to coronary heart disease during the 11 years of follow-up. The algorithms for identifying claudication [23], MI [24], stroke [21] and deaths due to coronary disease [24] have been reported previously. Secondary outcomes for this report included investigation of each of the following incident events separately: MI, silent MI, angina, CABG, angioplasty, claudication, stroke, TIA, as well as any coronary events and any cerebrovascular events. Coronary events included MI, CABG, angioplasty, angina, silent MI and deaths due to coronary disease. Cerebrovascular events included stroke and TIA.

2.4. Statistical analyses

A Cox hazards model with time dependent covariates was used to analyze the risk of developing cardiovascular events in users of ACEI/ARB compared to non-users, adjusting for potential confounders and possible significant interactions. Important risk factors for cardiovascular events were defined